DOCKET NO.: JJPR-0029
Application No.: 10/056,828
Office Action Dated: August 26, 2003

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
Plata-Salaman et al.

Application No.: **10/056,828**

Filing Date: **January 24, 2002**

Confirmation No.: **3409**

Group Art Unit: **1623**

Examiner: **T. McIntosh III**

For: **Treatment of Neurological Dysfunction Comprising Fructopyranose Sulfamates and Erythropoietin**

EXPRESS MAIL LABEL NO:
DATE OF DEPOSIT:

Mail Stop AF
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

DECLARATION OF CARLOS R. PLATA-SALAMAN PURSUANT TO 37 C.F.R. §1.132

I, Dr. Carlos R. Plata-Salaman, being duly warned that willful false statements and the like are punishable by fine or imprisonment or both (18 U.S.C. § 1001), and may jeopardize the validity of the patent application or any patent issuing thereon, state and declare as follows:

1. All statements herein made of my own knowledge are true, and statements made on information or belief are believed to be true and correct.

2. I, Dr. Carlos R. Plata-Salaman, am currently Senior Director of Scientific Licensing in the Pharmaceuticals Group Business Development, Johnson and Johnson Pharmaceutical Services, L.L.C.

3. In 1984, I, Dr. Carlos R. Plata-Salaman, graduated from the Faculty of Medicine of the University of Guadalajara, Mexico with a Medico Cirujano (Physician

Surgeon) degree, and in 1988, I graduated from Kyushu University, Japan with a Doctorate of Medical Science. A copy of my résumé is attached hereto as Exhibit B.

4. The present invention provides for the first time methods of treating neurological dysfunction comprising administering to a subject a therapeutically effective amount of a fructopyranose sulfamate and erythropoietin in an amount selected to produce a synergistic effect. The present invention also provides pharmaceutical compositions comprising topiramate and erythropoietin and processes for making such pharmaceutical compositions.

5. I am a named inventor on the above-referenced patent application. I have read and I am familiar with the contents of the patent application. In addition, I have read the Office Action dated August 26, 2003, received in the present case. It is my understanding that the Examiner believes that the combined teachings of Shank *et al.* (WO 00/61138 A1), Sachdeo (Topiramate: Clinical Profile in Epilepsy, Clin Pharmacokinet, May 1998, 34(5):335-346), and Brines *et al.* (WO 00/61164) render obvious the invention of the present application. In particular, it is my understanding that the Examiner believes that references that individually teach the use of a fructopyranose sulfamate or erythropoietin for the treatment of neurological disorder make the present application unpatentable because the Examiner believes that if agents are individually used to treat neurological disorders, it would be obvious to administer them concomitantly to treat neurological disorders.

6. There are compelling reasons why one of skill would not agree with the Examiner's conclusions. Prior to the invention described in our patent application, there was no precedent in any form for a combination therapy of topiramate and erythropoietin for the treatment of neurological disorders. The underlying reason for this lack of precedent is that topiramate and erythropoietin are very different classes of molecules and have distinct features as they relate to chemistry, mechanism of action, pharmacokinetics and current clinical uses. The following table, Table 1, exemplifies the different properties of the two drugs.

DOCKET NO.: JJPR-0029
Application No.: 10/056,828
Office Action Dated: August 26, 2003

TABLE 1

	Topiramate	Erythropoietin
Type	Fructopyranose sulfamate.	Glycoprotein. PROCRIT® is a 165 amino acid glycoprotein manufactured by recombinant DNA technology that has the same biological effect as endogenous erythropoietin.
Molecular Weight	339 daltons	30,400 daltons
Known Mechanism of Action	Sodium channel blocking action; enhancement of GABA activation of GABA-A receptors; inhibition of the AMPA and kainate subtype of glutamate receptors; inhibition of L-type calcium channels; carbonic anhydrase (CA-II and CA-IV) inhibition.	Enhances red blood cell production by stimulating the division and differentiation of committed erythroid progenitors in the bone marrow. Mechanism for proposed neurological activities has not been characterized.
Administration	Orally.	Intravenously or subcutaneously.
Half-Life	20-30 hours after oral administration.	3-11 hours after intravenous administration.
FDA approved indications	Topiramate (as TOPAMAX®) is indicated for use as adjunctive therapy for adults and pediatric patients aged 2-16 years with partial onset seizures, or primary generalized tonic-clonic seizures; and in patients 2 years of age and older with Lennox-Gastaut syndrome.	Treatment of anemia associated with chronic renal failure; treatment of anemia related to zidovudine therapy in HIV-infected patients; treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of chemotherapy; treatment of anemic patients scheduled to undergo elective, noncardiac, or nonvascular surgery to reduce the need for allogeneic blood transfusions; *not currently approved for treatment of neurological or neurodegenerative disorders.*

DOCKET NO.: JJPR-0029
Application No.: 10/056,828
Office Action Dated: August 26, 2003

7. Treatment of neurological and neurodegenerative disorders can involve adjunctive or combination therapy utilizing two or more drugs. However, this concomitant therapy needs a specific rationale, and one of skill in the art would not assume that two drugs that are effective when given individually would work better, or even as well, when administered together. Accordingly, one of skill in the art, when developing a rationale for concomitant therapy, would look to the characteristics of each individual compound, for instance, mechanism of action and pharmacokinetic and metabolic features of the respective compounds.

8. In evaluating the disparate properties of topiramate and erythropoietin as shown in Table 1, one of skill in the art would not be motivated to combine these two drugs. There is no *a priori* support for the notion that two drugs with such different properties would work together to provide even an equivalent effect, let alone a *synergistic* effect (a synergistic effect is one in which the effect of the combination is greater than the sum of each of the effects taken separately) in the treatment of neurological disorders.

9. Thus, Table 1 demonstrates that topiramate and erythropoietin are two very different molecules with distinct properties and it is not obvious to one of skill in the art that a synergistic response would be expected from the combination of topiramate and erythropoietin. Therefore, the discovery that concomitant administration of the two drugs provides a *synergistic* effect was an unexpected and surprising result.

10. Referring now to the references that have been cited in the current office action, those references provide no reason for one to expect that topiramate and erythropoietin would work together to provide a synergistic effect when concomitantly administered. This is because nowhere in the cited art does it suggest that topiramate and erythropoietin have properties that would indicate that they would work together to provide a synergistic effect.

11. In view of the foregoing, it is my scientific opinion that the references cited by the Examiner together do not suggest the combined use of a fructopyranose sulfamate and erythropoietin for the treatment of neurological dysfunction, nor do they suggest that the

DOCKET NO.: JJPR-0029
Application No.: 10/056,828
Office Action Dated: August 26, 2003

combination of these two treatments would result in a synergistic response. It is my scientific opinion that it would not be obvious to one of skill in the art of treating neurological or neurodegenerative disorders that two drugs that are effective when administered individually and have properties as divergent as topiramate and erythropoietin would, when administered concomitantly, provide a synergistic effect.

Date: 26 January 2004 By: Carlos R. Plata-Salamán

Dr. Carlos R. Plata Salaman